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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/733,756	12/08/2000	David Mack	A-69439/DJB/JJD	2798

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EXAMINER	
GOLDBERG, JEANINE ANNE	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 07/27/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/733,756	MACK ET AL.	
	Examiner	Art Unit	
	Jeanine A Goldberg	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 April 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,8-30,32,33,37,41-47 and 52-57* is/are pending in the application.

4a) Of the above claim(s) *1-6 and 8-30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *32-33, 37, 41-47, 52-57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the papers filed April 23, 2004

2. All arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow. This action is **FINAL.**

3. Any objections and rejections not reiterated below are hereby withdrawn in view of applicant's arguments, and the amendments to the claims.

4. Claims 32-33, 37, 41-47, 52-57 have been examined on the merits.

5. Claims 1-6, 8-30 have been withdrawn from consideration as drawn to non-elected claims.

Maintained Rejections

Claim Rejections - 35 USC § 112- Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 32-33, 37, 41-47, 52-57 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of determining a predisposition of an individual to colorectal cancer by determining the expression of SEQ ID NO: 1 in a first colorectal sample and comparing expression to a normal sample wherein an increase in expression is indicative of colorectal cancer, does not reasonably provide enablement for a method of detecting colorectal or breast cancer by determining the expression of a nucleic acid that encodes an amino acid sequence of SEQ ID NO: 2. The specification does not enable any person skilled in the art to which

it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The claims are broadly drawn to a method for detecting breast cancer or colorectal cancer by determining the expression level of a nucleic acid sequence that encodes an amino acid sequence of SEQ ID NO: 2.

The specification teaches that SEQ ID NO: 1 corresponds to the gene CHA4. CHA4 nucleic acid and amino acid sequences are shown in Figure 1 and 2, respectively. Example 3, states that expression studies were performed using an oligonucleotide array. The biochip contained the sequence shown in accession number T32108. Figures 3A illustrates the relative amount of expression of CHA4 in various samples of breast cancer tissue; Figure 3B illustrates colorectal cancer tissue; and Figures 3C-3D illustrate several normal tissue types. With respect to Figure 3A directed to breast cancer tissue, the expression level in the tissues appears to range from 100-750 (no units provided). Turning to Figure 3C, normal breast tissue appears to range

from 80-400 (no units provided). As seen in Figure 3A, 54 of the samples had expression within the "normal" range of expression. 54 of the 66 (83%) breast cancer tissues had expression levels less than 400. Therefore, there does not appear to be differential expression between the breast cancer tissues of Figure 3A and the 7 breast normal tissues of Figure 3C.

With respect to Figure 3B directed to colorectal cancer tissue, the expression level in the numerous tissues appears to range from 100-740 (no units provided). Turning to Figure 3C, normal colon appears to range from 100-200. 11 of the 78 (14%) colorectal tissues had expression levels less than 200. Therefore, the ranges of normal and cancerous expression levels of CHA4 overlap.

The art teaches what is called CHA4 in the specification has also been referred to as Ephrin-A3, EphA3, hek-L, Lerk-3, ehk1-L, and Ehk1. Beckmann et al. (US Pat. 5,516,658, May 1996) teaches Hek ligand (hek-L) polypeptides and nucleic acids encoding the polypeptides. The Hek-L polypeptides, SEQ ID NO: 2 of Beckmann and SEQ ID NO: 2 of the instant application are 100% identical over all 238 amino acids. The nucleic acid of Beckmann, namely SEQ ID NO: 1 and the instant SEQ ID NO: 1 share 52.7% identity over the full length with a best local similarity of 99.8% (see attached alignment). Beckmann teaches a human T-cell leukemia cell line expresses the Hek-L nucleic acid. Beckmann does not specifically teach using the Hek-L for diagnostic of cancers.

Neither the specification nor the art teach the skilled artisan how to use the invention as broadly as claimed. The specification and claims of the instant application

assert that detection of the expression of a nucleic acid that encodes an amino acid sequence of SEQ ID NO: 2 allows for diagnosis of colorectal cancer. The evidence for this assertion provided in the specification, in Figure 3A-3D, Example 3, page 68, does not appear to support the assertion. As provided in the analysis above, the ranges for "normal" and "cancerous" tissue expression of CHA4 overlap in both breast and colon cancers analyzed. There is no indication in the specification of a threshold which would be indicative of colon or breast cancer tissue. Therefore, distinguishing a cancerous tissue from a normal tissue based solely on different sample expression would be unpredictable. While one could conduct additional experimentation to determine whether, e.g., expression of SEQ ID NO: 1 at certain levels might be associated with, e.g., certain types of colorectal or breast cancers, the outcome of such research cannot be predicted, and such further research and experimentation are both unpredictable and undue. Specifically, 83% of the breast cancer tumors were within the "normal range."

Furthermore, the teachings of the prior art do not provide evidence of how to use the methods in which expression of a nucleic acid that encodes an amino acid sequence of SEQ ID NO: 2 are an indicator of breast or colorectal cancer. A nucleic acid that encodes an amino acid sequence of SEQ ID NO: 2 is not limited to any particular sequence, but comprises nucleic acid degenerates or fragments that encode part of SEQ ID NO: 2. The original claims were drawn to detecting a nucleic acid with at least 75% identity with SEQ ID NO: 1. The specification does not teach any analysis of variants of a nucleic acid that encodes an amino acid sequence of SEQ ID NO: 2. These variants may include variants which afford a protective effect to the nucleic acid

such that they are indicative of lower risk for cancer. The variants also include splice-variants, SNPs, mutations, deletions, insertions which may have different diagnostic implications on the nucleic acids. Without undue and unpredictable experimentation, the skilled artisan would not be aware of which of the variants would have which effects on the risk of breast or colon cancers. It is unclear whether the nucleic acid encoding SEQ ID NO: 2, provided by Beckmann would have the same diagnostic effects as the instant SEQ ID NO: 1. As discussed briefly above, the specification asserts to have used an oligonucleotide array with T32108 as a probe. Based upon a visual inspection of T32108 appears to be most closely similar to nucleotides 1506-1690, while not 100% identical. Detection of nucleic acids which hybridize to T32108 is a much smaller class of compounds that nucleic acids which hybridize to a nucleic acid that encodes an amino acid sequence of SEQ ID NO: 2. Detection of a nucleic acid that encodes an amino acid sequence of SEQ ID NO: 2 encompasses nucleic acids which hybridize to the degenerate nucleic acid sequences of SEQ ID NO: 2. There is no indication that all of the degenerate nucleic acids sequences encoding SEQ ID NO: 2 would have the same diagnostics as T32108. Thus, since detection of a nucleic acid that encodes an amino acid sequence of SEQ ID NO: 2 is directed to nucleic acids non-specific hybridization would occur and would likely detect nucleic acid sequences which are not SEQ ID NO: 1 or T32108. The utility of the method is dependent on the specific nucleotide composition of the probe used to detect SEQ ID NO: 1 or nucleic acids that encode an amino acid sequence of SEQ ID NO: 2. Degenerate coding sequences of any of these sequences, however, would not necessarily hybridize to SEQ ID NO 1 or

would provide nonspecific hybridization such that the cancerous samples would not be differentiated from normal samples or any other tissue sample.

With respect to Claims 44-47, the specification does not teach how expression of a nucleic acid that encodes an amino acid sequence of SEQ ID NO: 2 are predictive of prognosis. The specification does not teach any levels of expression which provide extremely poor prognosis, as opposed to which levels of expression are deemed to be indicative of good prognosis. There are not thresholds or ranges which delineate any prognosis levels for individuals.

The teachings of the specification do not establish that one could actually detect expression of a nucleic acid that encodes an amino acid sequence of SEQ ID NO: 2 as an indicator of colorectal or breast cancer. Rather the teachings of the specification assert that a biochip comprising nucleotides 1506-1690 of SEQ ID NO: 1 illustrate expression at higher levels in the colon and breast tissue than in other human tissue types, as discussed above. In the absence of guidance from the specification, one skill in the art may look to the teachings of the prior art for enablement of a claimed invention. However, the closest prior art references, namely Beckmann, does not provide support for the use of expression of a nucleic acid that encodes an amino acid sequence of SEQ ID NO: 2 as an indicator of colorectal or breast cancer. Thus, it is unpredictable as to whether one could successfully use the claimed invention, and given the fact that neither the specification nor the prior art provide evidence of a correlation or association between a nucleic acid that encodes an amino acid sequence of SEQ ID NO: 2 expression and colorectal or breast cancer, it is further unpredictable

as to whether any quantity of experimentation would allow one to practice the claimed invention. Accordingly, it would require undue experimentation for a skilled artisan to use the claimed invention.

Response to Arguments

The response traverses the rejection. The response asserts that the examiner has indicated that the specification is enabling for a method of determining the predisposition of an individual to colorectal cancer by determining the expression of a nucleic acid that encodes an amino acid sequence of SEQ ID NO: 2. This is not what the examiner indicated was enabled. The rejection above states, "while being enabling for a method of determining a predisposition of an individual to colorectal cancer by determining the expression of SEQ ID NO: 1 in a first colorectal sample and comparing expression to a normal sample wherein an increase in expression is indicative of colorectal cancer."

The response points out that the claims are drawn to a method of detecting rather than diagnosing. The examiner appreciates the response pointing out this difference and has made the corrections to the statement above. This however, does not change the merits of the rejection. The examiner acknowledges that 100% accuracy is not required for detecting colorectal cancer or breast cancer, however for the reasons above, the method does not appear to enable the skilled artisan to use the method for detecting cancer. The claims have been amended to they are no longer definite (see 112/2nd below). It is unclear whether the method is for detecting cancer or for merely analyzing the sample which may or may not be useful.

With respect to the argument that the breast cancer data supports a method of detecting breast cancer, the response argues that 65% of the breast cancer tissue samples show elevated levels relative to the average CHA4 expression level observed in normal breast cancer issue samples shown in Figure 3C (response filed April 23, 2004, page 10). With respect to the evidence in the specification with respect to breast cancer, only 17% of the cancers had expression levels above normal (if normal is defined as the highest detected expression in a normal tissue- i.e. about 400). The examiner does not believe that the presence of an overexpression in 17% of the breast cancers is a significant result that the skilled artisan may use for detecting breast cancer. Thus, in overwhelming majority of the cancers tested, accurate and predictable results would not be observed.

The response has reviewed the data in a different manner and asserts that if the average CHA4 expression level observed in normal breast cancer tissue is analyzed, 65% of the cancers showed elevated levels. The instant specification fails to provide any analysis of the data provided in Figures 3A-3D. There is no indication of whether the expression levels varies between cancer and normal breast tissues in a meaningful way since at the time the invention was made no analysis was performed. Depending on how the data in the specification is analyzed and used, will greatly affect the outcome of the results. Applicant's arguments are limited to attorney arguments. The specification does not take the data in the specification and indicate how the results should be analyzed. The response argues that only 2/7 normal breast tissue samples had levels higher than 300. However, the instant specification and claims do not require

any particular threshold for assigning samples as tumor or normal. The response further asserts that an average value would be more appropriate value to rely up, however, this means of detection is neither claimed nor contemplated in the instant specification. The claim merely recites comparing expression levels, therefore, in the event that the normal being compared to was above 400, incorrect detection would be made in 83% of the cases. The response also compares two of the normal samples with corresponding tumor samples and concludes that the levels were lower in normal tissue. The specification fails to provide evidence for the other 5 normal breast tissues with respect to the expression levels in the corresponding tumor tissues, particularly, the highly expressed normal tissues, for example, Breast 100DOY and Breast-2. In the event that each of these is more highly expressed in tumors cells, a secondary consideration may be found. However, based upon the evidence as a whole in the specification, detecting breast cancer using this method would not enable the skilled artisan to make and use the invention at the time of filing.

The response asserts that "the overlapping ranges of mRNA expression in cancerous versus normal tissues that the examiner finds problematic are also observed for the well-recognized breast cancer biomarker, HER2." This argument has been thoroughly reviewed, but is not found persuasive because there is no analysis or evidence on the record whether the mechanisms of HER2 and CHA4 are similar. HER2 has been thoroughly examined in the art and the expression levels of HER2 are not claimed in the instant claims.

The response asserts that the method does not have to be commercially viable. This argument has been thoroughly reviewed, but is not found persuasive because the rejection is not requiring an absolute method. The requirement for enablement is that the method must be predictable and useful. It is unpredictable that when the skilled artisan takes a breast tissue sample and a normal breast tissue that the breast cancer tissue will be increased expression of SEQ ID NO: 1. As discussed above, the instant specification did not set forth any analysis of the data to illustrate that the skilled artisan could use this method to detect breast cancer. MPEP 716.01(c) makes clear that "The arguments of counsel cannot take the place of evidence in the record. In re Schulze , 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965).

The response asserts that the examiner has speculated that "slice variants, SNPs, mutations, deletions, insertions may exist that may have different diagnostic implications on the nucleic acid and that no indication that degenerates would have the same diagnostics as T32108" (page 12 of response filed May 23, 2004). This argument has been thoroughly reviewed, but is not found persuasive. The examiner has provided evidence of splice variants and different sequences which each encode SEQ ID NO: 2. As stated above, the Hek-L polypeptides, SEQ ID NO: 2 of Beckmann and SEQ ID NO: 2 of the instant application are 100% identical over all 238 amino acids. The nucleic acid of Beckmann, namely SEQ ID NO: 1 and the instant SEQ ID NO: 1 share 52.7% identity over the full length with a best local similarity of 99.8% (see attached alignment). Therefore, there is evidence of record there are either splice variants, SNPS, mutations etc within the Hek-L and CHA4 genes. Furthermore, the specification specifically

suggests that the amino acid sequence for Ephrin-A3 is nearly identical to the amino acid sequence for EHK1 such that the two proteins are possibly the result of mRNA splice variants of the same gene. The applicant's own specification suggests and contemplates that there are splice variants within the instant gene. Therefore, the objective evidence on the record suggests that there are splice variants, mutations and SNPs within the gene. It is unpredictable that each of these variations in the gene at the nucleic acid level all have the same association with disease. It is well known in the art that differences in the DNA sequence at the level of splice variants, mutations and SNPs have different diagnostic effects. The skilled artisan could not practice the claimed invention as broadly as claimed without further, undue experimentation to determine whether these variations could be used to detect cancer.

The response asserts that Claims 44-47 have been amended to recite determine prognosis of the individual based upon a high level of expression at different cellular states may indicate a poor prognosis. This correlation has not been established in either the specification nor the art. The specification is completely silent with respect to poorer prognosis based upon the increased expression of CHA4 or a low level of expression as prognostic of poorer prognosis. The specification fails to set forth what "a high level of expression encompasses." The evidence of record, fails to provide any guidance with respect to prognosis based upon the detection of expression levels, for the reasons set forth above.

Thus for the reasons above and those already of record, the rejection is maintained.

New Grounds of Rejection Necessitated by Amendment

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 32-33, 37, 41-47, 52-57 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 32-33, 37, 41-47, 52-57 are indefinite over the recitation "may indicated colorectal cancer." The claim is unclear whether the claim is drawn to a method of detecting cancer or whether the claims are drawn to performing expression analysis which may indicate cancer. As written, the claim has become unclear. A method of detecting a predisposition to colorectal cancer by determining expression and comparing expression wherein increased expression...is indicative of increased predisposition to cancer, for example would appear to be more appropriate claim language based upon applicants arguments. Claims 44 and 52 have been similarly amended to require "may indicate."

B) Claims 44-47 have been amended to recite "a high level of expression." The term "high" in claim 44 is a relative term which renders the claim indefinite. The term "high" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is unclear whether high level is any level above the normal range, whether the high level is anything above the "average" or

whether high is some other undisclosed range. Furthermore, "poor prognosis" is unclear. It is unclear whether poor prognosis is the detection of cancer such that the individual lives with cancer, whether poor prognosis is a predicted amount of time the patient is expected to live or poor prognosis is the amount of recovery and treatment is required. Poor is also a relative term. Thus, the metes and bounds of the claims are unclear.

Conclusion

8. No claims allowable.

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (571) 272-0743. The examiner can normally be reached Monday-Friday from 7:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (571) 272-0782.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

J. Goldberg

Jeanine Goldberg
Patent Examiner
July 23, 2004